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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/004,306	10/23/2001	Brian R. Dixon	5048PIC1D1	8710

7590

02/06/2003

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EXAMINER

MCKENZIE, THOMAS C

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 02/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/004,306

Applicant(s)

DIXON ET AL.

Examiner

Thomas McKenzie Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 October 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 6-9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 709 is/are rejected.
- 7) ☒ Claim(s) 6 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 10/23/01. There are seven claims pending and seven under consideration. Claims 1-3 and 6 are compound claims. Claim 7 is a composition claim. Claims 8 and 9 are use claims. This is the first action on the merits. The application concerns some 2-imino-1,3-oxazolidine compounds, compositions, and uses thereof.

Priority

2. The status of non-provisional parent application should also be included. When a parent application has become a patent, the expression "now Patent No. 6,353,006" should follow the filing date of the parent application.

Title

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacing the word "Heterocycles" by --Oxazolidines--.

Abstract

4. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The

abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The abstract is too short and generic. Examiner suggests claim 1, lines 1-15 including the figure, and the utility.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 6 Applicants claim the substituent "heteroaryl". The substituent "T" is mandatory (t = 1-5), yet "aryl" and "heteroaryl" cannot be substituted. To quote from Streitwieser (Introduction to Organic Chemistry) says on page 649, second paragraph "[a]romatic hydrocarbons have the generic name of arene. [a]ccordingly, for many purposes the abbreviation Ar, for aryl is used just as R is used for alkyl...". The Examiner suggests using "substituted heteroaryl wherein the substituent are selected from ...".

6. Claims 2 and 3 recites the limitation "substituted pyridyl" in line 6. There is no antecedent basis for this limitation in the parent claim, which claims "heteroaryl". The reasoning is discussed above.

7. Claims 1-3 and 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In proviso a), claims 1-3 recites the limitation "(Q)_qR¹". There is no antecedent basis for this limitation in the claim, which claims "(G)_qR¹".

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other listed diseases, does not reasonably provide enablement for "C8) enhancement of female sexual receptivity and male sexual receptivity, C11) improvement of short term memory, C16) prevention of myocardial infarction, H1) promotion of myelin repair or E1) treatment of cancer" generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Rosen in his review "Prosexual Drugs: Empirical Status of the "New Aphrodisiacs" said in the abstract "no single drug has proven to be clinically safe and reliably effective for human use". Burke in his review "Update on

Alzheimer's disease" on pages 90-96, final paragraph lists cholinesterase inhibitors, vitamin E, estrogen, and nonsteroidal anti-inflammatory drugs as possible treatments of the symptoms of Alzheimer's disease. There is no mention of either the 2-imino-oxazolidines of the present application or of progesteronal agents generally. Mehta in his review "Secondary Prevention in Acute Myocardial Infarction" lists β -blockers, aspirin, lipid lowering agents, and angiotensin converting enzyme inhibitors as the only currently established methods of preventing heart attacks generally, not the agents of the present application. Mylin repair would embrace treatment of multiple sclerosis. Polman (BMJ) reports in the table on page 492 that interferon is the only established therapy for multiple sclerosis. Glatiramer acetate is a second line treatment used in the US but not Europe. Progesterone receptor inhibitors are not presently known to be efficacious for this purpose. Thus, the skilled clinician would not know how to use them to treat MS with Applicants' compounds.

Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics*, 211 USPQ 907, *In re Langer*, 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement

requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

In the present Application there is no data concerning any *in vitro* or *in vivo* art recognized models for "C8) enhancement of female sexual receptivity and male sexual receptivity, C11) improvement of short term memory, C16) prevention of myocardial infarction, H1) promotion of myelin repair or E1) treatment of cancer". Compounds with the structure of those of claims 1-3 and 6 or with Applicants' postulated mechanism of action have not been shown efficacious in these therapeutic arts. Thus, Applicants lack any working examples of such claimed use and lack enablement for such disease treatment claims.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. Determining if any of Applicants' compounds was capable of treating a specific human disease would clinical trials, a large amount and potentially inconclusive experimentation. The direction concerning clinical usage

of Applicants compounds is found in lines 19-30 on page 21. There are no working examples concerning the clinical efficacy of any of Applicants' compounds. The state of the art is summarized above. The artisan using Applicants invention would be a physician with a MD degree and several years of clinical experience. The clinical and biological arts are inherently unpredictable, *In re Fisher* 166 USPQ 18, *In re Wright* 27 USPQ2d 1510, *In re Vaeck* 20 USPQ2d 1438.

9. Claims 8 and 9 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specifically listed cancers, does not reasonably provide enablement for all cancers generally. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

To make clearer the lack of enablement for treatment of all cancer, extrinsic evidence is supplied by Draetta (Ann. Reports Med. Chem.), final sentence on page 246 "Although many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease

make the prospect of developing such a universal cure very unlikely." Since no universal cure for cancer has been developed, it follows that there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims.

The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

Claim Rejections - 35 USC § 102

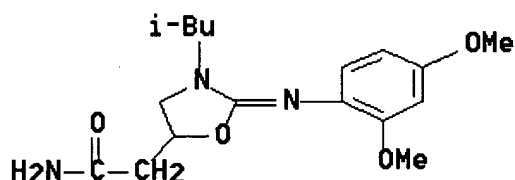
10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

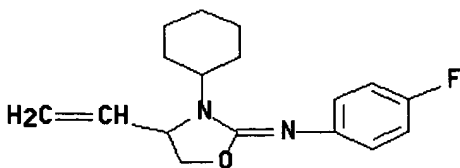
- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(a) as being anticipated by Goff (Tetrahedron Letters). The compound shown below fits the formula of claim 1 with T = OMe, t = 2, R = 2,4-substituted-phenyl, n = 2, R¹ = 2-methylpropyl, g =

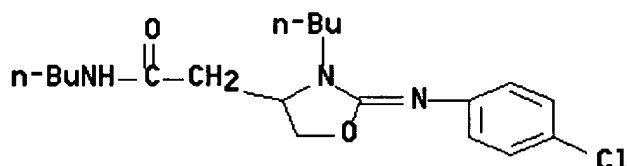
0, R^2 = ethyl, q = 3, first Q = NH_2 , second and third Q = oxo and X = oxygen. It has Registry Number 204330-14-3 and is found in Scheme 2, page 1479 of the reference and is compound **5a**. Synthesis is described in the penultimate sentence in the first paragraph on the cited page.



11. Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Larksarp (Journal of Organic Chemistry). There are nine compounds disclosed in this reference including the compound shown below that fit the formula of claim 1. The compound below has T = fluorine, t = 1, R = 4-substituted-phenyl, n = 2, R^1 = cyclohexyl, g = 0, R^2 = ethylene on position 4 of the oxazolidine ring, q = 0, and X = oxygen. It has Registry Number 212687-20-2 and is found in Equation 2 and Table 1 on page 6230 of the reference. It is compound **7f**. Compounds **7g** and **7e** are pictured on page 6231 of the reference.

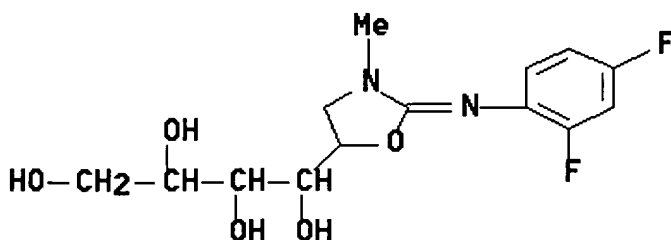


12. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Tyukhteneva (Khimiya Geterotsiklicheskikh Soedinenii). The compound shown below fits the formula of claim 1 with T = chlorine, t = 1, R = 4-substituted-phenyl, n = 2, R¹ = butyl, g = 0, R² = ethyl on position 4 of the oxazolidine ring, q = 3, first Q = NHBu, R⁶ = hydrogen, R⁷ = butyl, second and third Q = oxo, and X = oxygen. It has Registry Number 104053-32-9 and is found in the diagram on page 1629 of the reference. It is compound IV_B and physical properties are found in the eighth entry in the table on the following page of the reference.



Allowable Subject Matter

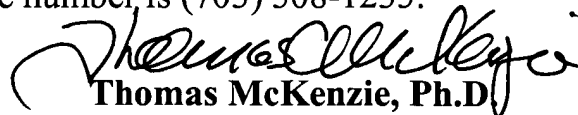
13. Claim 6 is objected to as being dependent upon a rejected base claim. Claim 7 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: Claims 1, 2, and 6 are patentable over Qian (CN 1,294,126 A). There are three compounds disclosed in this reference including the compound shown below that fit the formula



of claim 1. The compound below has T = fluorine, t = 2, R = 2, 4-substituted phenyl, n = 2, R¹ = methyl, g = 0, R² = butyl, q = 3, Q = OH, and X = oxygen. It is found in the last line on page 12 of the reference. However, Applicants' effective filing date of 1999 makes Qian (CN 1,294,126 A) an incompetent reference.

Conclusion

14. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.


Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
February 4, 2003

